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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,335	06/13/2001	Hermann-Joseph Grone	P/717-189	9473

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EXAMINER
HAMUD, FOZIA M

ART UNIT	PAPER NUMBER
1647	9

DATE MAILED: 02/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File copy

Office Action Summary

Application No.	Applicant(s)
09/787,335	Grone et al.
Examiner	**Art Unit**
Fozia Hamud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Dec 6, 2001*.

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *17-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *17-37* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [X] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) [X] Notice of References Cited (PTO-892)
16) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) [X] Information Disclosure Statement(s) (PTO-1449) Paper No(s). 9
18) [ ] Interview Summary (PTO-413) Paper No(s). ___
19) [ ] Notice of Informal Patent Application (PTO-152)
20) [ ] Other:

DETAILED ACTION

1. Claims 1-16 have been canceled and new claims 17-37 have been entered in Paper No:8, filed on 06 December 2001. Thus claims 17-37 are pending and under consideration by the Examiner.

2. Because Applicants have canceled original claims 1-16, the office action mailed on 06 November 2001 in Paper No:7 is moot and should be replaced with this office action.

Specification

3a. It is noted that this application appears to claim subject matter disclosed in prior PCT Application No. PCT/EP99/06844 filed on 16 September 1999, now WO 00/16796 issued on 30 March 2000. A reference to the prior application must be inserted as the first sentence of the specification of this application if Applicant intends to rely on the filing date of the prior application under 35 U.S.C. 120. See 37 CFR 1.78(a).

It is suggested that below the title of the invention be inserted:

Cross Reference to Related Applications

"This Application is a 371 of WO 00/16796".

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 17-37, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating or preventing the rejection of renal allograft

transplantation by administering a pharmaceutical composition comprising the chemokine receptor antagonist Met-RANTES and cyclosporin and a pharmaceutical composition comprising Met-RANTES and cyclosporin, does not reasonably provide enablement for a method of treating or preventing the rejection of transplanted organs, tissues or cells by administering a pharmaceutical composition comprising "all possible" chemokine receptor antagonists and cyclosporin or a pharmaceutical composition comprising "all possible" chemokine receptor antagonists and cyclosporin, or wherein said chemokine receptor antagonist is amino-terminally truncated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 17 and 30 recite "a method of treating or preventing the rejection of transplanted organs, tissues or cells by administering a chemokine receptor antagonist in combination with a cyclosporin ....." and "a pharmaceutical composition comprising ... a combination of a chemokine receptor antagonist and a cyclosporin ", respectively, what is claimed in the instant invention broadly encompasses pharmaceutical compositions comprising "all" chemokine receptor antagonists in combination with a cyclosporin and a method of using said pharmaceutical composition for treating or preventing the rejection of transplanted organs, tissues or cells. While the specification discloses that Met-RANTES in combination with low dose of cyclosporin caused significant reduction of interstitial rejection of renal allograft transplantation, significant reduction in the vascular and tubular damage and significant reduction in mononuclear cell infiltration, (see page 4, lines 16-27, page 16, lines 11-27 and table 2 and 3). Thus the only chemokine receptor antagonist used in combination with cyclosporin for the treatment and prevention of the rejection of transplanted kidney, is Met-RANTES.

The physiological effects of chemokines receptors are diverse, and one of ordinary skill in the art would not expect antagonism of any chemokine receptor to result in the reduction of graft rejection. Therefore, the specification is non-enabling for the unlimited number chemokine receptor antagonists (amino-terminally truncated, extended or full length) encompassed by the scope of the claims to be used in combination with cyclosporin, because not all chemokine receptors are involved in the rejection of transplants. The claimed invention encompasses chemokine receptor antagonists not envisioned or described in the specification, and neither does the specification disclose whether these claimed chemokine receptor antagonists in combination with cyclosporin would have beneficial or detrimental effects on organ transplant patients. The specification discloses that adding a single methionine at the N-terminus of RANTES changes the agonist protein into a RANTES receptor antagonist with nonmolar potency, and that treatment of rat renal transplant model with Met-RANTES in combination with low dose of cyclosporin caused a significant reduction of interstitial rejection in renal allograft transplantation, (page 16). Thus the only amino-terminally extended chemokine receptor antagonist to be used in combination with cyclosporin, disclosed by Applicants is Met-RANTES. The specification describes the specific chemokine receptor antagonist Met-RANTES which has specific characteristics and properties. These properties differ structurally, chemically and physically from other known chemokine receptor antagonists. The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant application, the only chemokine receptor antagonist disclosed and used in combination with cyclosporin for the treatment and prevention of renal transplant rejection is Met-RANTES, and the skilled artisan would not be able to predict if other chemokine receptor antagonists in combination with cyclosporin would have any significant effect on organ transplant rejection, whether they would have beneficial or detrimental effects on patients. There is no guidance that "all" chemokine receptor antagonists would function the way Met-RANTES did, neither does the specification provide any guidance of how many amino acids to delete from the N-terminus, how many amino acids to add to the N-terminus of said chemokine receptor antagonists. Furthermore, instant specification only demonstrates that Met-RANTES in combination with low dose of cyclosporin caused significant reduction of interstitial rejection of renal allograft transplantation, and does not show that said pharmaceutical composition would be effective against rejection of other transplanted organs, tissues or cells.

With respect to claims 23 and 34, Applicants have not demonstrated that "a metabolite or synthetic analogue" of cyclosporin A, when used in combination with a chemokine receptor antagonist was effective in preventing or treating the rejection of transplanted organs, tissues or cells. Applicants only showed that a combination of Met-RANTES with cyclosporin A was effective against rejection of renal allograft transplantation. Therefore, unless one of ordinary skill in the art would predictably substitute the " metabolite or synthetic analogue", recited in claims 23 and 34 with cyclosporin, expecting the same result and mode of action, this limitation is not enabled.

Thus, Applicants are only enabled for a method of treating or preventing the rejection of renal allograft transplantation by administering a pharmaceutical composition comprising the chemokine receptor antagonist Met-RANTES in combination with cyclosporin and a pharmaceutical composition comprising Met-RANTES and cyclosporin.

Claim rejections-35 U.S.C. § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5a. Claims 17-19, 21-30, 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pattison et al (1994) in view of Proudfoot et al. (1996) and further in view of Matindale (1996).

Pattison et al teach that RANTES (a chemokine which is specifically chemotactic for T-cells, monocytes and eosinophils), is expressed during cell-mediated transplant rejection of the kidney. RANTES expression by in-situ hybridization and the distribution of RANTES protein by immunohistochemistry, were studied in renal allograft biopsy specimens with varying severity of acute cellular rejection, samples from cardiac transplant recipients with cyclosporin nephrotoxicity and samples taken one hour after transplantation, (see abstract and page 209, column 2). The researchers

demonstrated that RANTES was not expressed in samples taken one hour after transplantation or in native renal biopsy taken from cardiac transplant patients with cyclosporin nephrotoxicity, but was detected in 17 of 20 biopsy specimen from kidneys with cellular rejection, (see page 210, column 1). Pattison et al suggest that RANTES has a role in allograft rejection and may be a prime target for immunomodulation in transplant rejection and other immune-mediated diseases. However, Pattison et al do not disclose a method of treating or preventing the rejection of transplant organs, tissues or cells by administering a chemokine receptor antagonist and cyclosporin or a pharmaceutical composition which comprises RANTES antagonist and cyclosporin.

Proudfoot et al teach that extension of recombinant human RANTES by a single residue at the amino terminus is sufficient to produce a potent and selective RANTES antagonist, (see abstract). The researchers demonstrated that Met-RANTES, unlike naturally isolated RANTES or full-length recombinant RANTES was unable to cause chemotaxis or calcium mobilization in the promonocytic cell line THP-1, and that it actually antagonized the ability for RANTES to stimulate chemotaxis of THP-1 cells with an IC50 value of 6 nM, (see page 2600, column 2 and figure 2).

Martindale teaches that cyclosporin is a powerful immunosuppressant with a specific action on T-lymphocytes, (depresses T-cell proliferation). Cyclosporin is given orally or intravenously for the prophylaxis of graft reaction in organ and tissue transplantation, (see page 557, column 1). Martindale teaches that adverse reactions of cyclosporin treatment include, nephrotoxicity and that in renal graft patients episodes of nephrotoxicity may be difficult to distinguish from graft rejection, (see page 557, bottom of column 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention, to design a method of treating or preventing the rejection of transplanted kidney by administering the Met-RANTES peptide disclosed by Proudfoot to a kidney transplant patient, because Pattison et al teach that RANTES has a role in kidney allograft rejection and demonstrated that RANTES is expressed in biopsy specimens from kidneys with cellular rejection, since Met-RANTES would inhibit T-cell migrtation caused by RANTES in kidney transplant patients. It would also have been obvious to one of ordinary skill in the art at the time of the instant invention to combine cyclosporin and Met-RANTES to treat or prevent kidney transplant rejection, or to make a pharmaceutical composition which comprises cyclosporin and Met-RANTES, because Martindale teaches that cyclosporin is a powerful immunosuppressant routinely used for graft rejection, with a specific action on T-lymphocytes proliferation.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine a RANTES antagonist and cyclosporin for the treatment or prevention of transplanted kidney or to design a pharmaceutical composition which comprises RANTES antagonist and cyclosporin for the treatment or prevention of transplanted kidney, because RANTES antagonist would prevent the migration of T-cells stimulated by RANTES and cyclosporin would inhibit T-cell proliferation. Since acute renal allograft rejection is characterized by a mononuclear cell infiltrate which consists mainly of T-lymphocytes (see specification pages 1-2), inhibiting both T cell migration and proliferation would be a very effective way to treat or prevent renal allograft rejection because the combination of RANTES antagonist and cyclosporin would have synergistic effect on T cell

actions. Furthermore, combining said compositions would ensure the use of low dose cyclosporin, thus overcoming the problems associated with high dose cyclosporin, such as nephrotoxicity.

Conclusion

6. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday, Wednesday-Thursday from 6:30AM to 4:00PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
31 January 2002

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